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ORIGINAL ARTICLE

Synthesis of novel isoxazolines and isoxazoles of N-substituted pyrazolo[3,4-*d*]pyrimidin-4(5H)-one derivatives through [3 + 2] cycloaddition

Ameur Rahmouni [a], Anis Romdhane [a], Abderrahim Ben said [a], Vincent Guérineau [b], David Touboul [b], Hichem Ben Jannet [a,*]

[a] *Laboratoire de Chimie Hétérocyclique, Produits Naturels et Réactivité, Equipe: Chimie Médicinale et Produits Naturels, Faculté des Sciences de Monastir, Université de Monastir, Avenue de l'Environnement, 5019 Monastir, Tunisia*
[b] *Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France*

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1,3-dipolar cycloaddition;
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Isoxazoles

Abstract 3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **3** was prepared by an intramolecular cyclization of *N*-(4-cyano-3-methyl-1-phenyl-1*H*-pyrazol-5-yl) acetamide **2** in ethanol in the presence of piperidine. *N*-allylation and *N*-propargyl alkylation of *N*-substituted pyrazolo[3,4-*d*] pyrimidin-4(5*H*)-one **3** yielded the corresponding dipolarophiles **4** and **5** which afford by condensation with arylnitrile oxides in toluene the expected new isoxazolines **6** and isoxazoles **7**, respectively. On the other hand, the aminopyrazole **1** in refluxing with ethanol in the presence of sodium hydroxide afforded the corresponding carboxamide **8**, which then, was converted to its ethyl 3-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*] pyrimidine-6-carboxylate **9** with neat diethyl oxalate. The dipolarophile **10** on regiospecific *1,3*-dipolar cycloaddition with arylnitrile oxides affords isoxazoles **11** and the unexpected deethoxycarbonylated isoxazoles **12**. The target compounds were completely characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS.

1. Introduction

Heterocycles display an array of significant bioactive properties (Penning et al., 1997; Quiroga et al., 2008a,b) and are present in a wide variety of drugs (Mekheimer et al., 2012). Among the family of heterocyclic compounds, isoxazoles and isoxazolines are an important class of five membered ring system, displaying a wide variety of biological properties including antiviral (Lee and Kim, 2002), antidepressant (Krompiec et al., 2008) and anti-inflammatory activities (Dadiboyena

* Corresponding author. Tel./fax: +216 73500278.
E-mail address: hichem.benjannet@yahoo.fr (H. Ben Jannet).
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and Nefzi, 2012). In fact, the isoxazolines possess significant synthetic applications (Vilela et al., 2011), diverse biological properties (Soro et al., 2006) and represent a unique class of pharmacophore present in many therapeutic agents (Maheswari and Perumal, 2012). Also they showed, anti-tubercular (Rakesh et al., 2009), antifungal (Basappa et al., 2003) and anti-influenza effects (Kai et al., 2001). On the other hand, isoxazole structural motif is found in the COX II inhibitors, bextra and parecoxib because of its capability to exhibit a wide range of bioactivities, including the anti-inflammatory and antimicrobial activities (Dadiboyena and Nefzi, 2010; Sobenina et al., 2005). For these reasons the synthesis of this family of heterocycles continues to attract the attention of synthetic organic and medicinal chemists.

A plethora of methodologies exist toward the synthesis of isoxazoles and isoxazolines and most of them endeavor nitrile oxide cycloaddition (NOC) as a key step (Cecchi et al., 2005; Conti et al., 2010). Literature reports that, the intermolecular [3 + 2] cycloaddition reaction of arylnitrile oxides with various alkenes and alkynes represents an efficient and convergent method for the construction of such compounds, while this strategy sometimes incurs problems in the yield and/or regio- or stereoselectivity of the reaction.

On the other hand, the chemistry of pyrazolopyrimidine and analogues has been a focus of intense research, due to their widespread occurrence in drugs (Holla et al., 2006) and their diversified biological activities (Dawood et al., 2008; Oliveira-Campos et al., 2007). We report that *N*-Substituted pyrazolopyrimidine derivatives have been extensively studied but to the best of our knowledge there is no report of any incorporating an isoxazoline or isoxazole moiety.

Taking into account the various biological activities of isoxazolines, isoxazoles and pyrazolopyrimidines cited in the literature, it appeared to us interesting to think about the combination of these moieties hoping to access to more biologically effective compounds.

As part of our continued interest in the development of efficient methods for the synthesis of biological heterocyclic compounds, we report herein a facile and efficient synthesis of novel pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones derivatives, incorporating the isoxazoline or isoxazole moiety, in good yields *via 1,3*-dipolar cycloaddition, in the hope they will be a potent biologically and pharmacologically compounds.

2. Results and discussion

Our first key intermediate was the 5-aminopyrazole-4-carbonitrile **1** which was easily prepared from condensation of ethoxymethylenemalonitrile with phenylhydrazine (Youssef et al., 2010). Compound **1** heated in acetic anhydride (El-Enany et al., 2010; Rashad et al., 2009) afforded *N*-(4-cyano-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)acetamide **2** in 75% which was identified on the basis of its spectral analyses. The $_1$H NMR spectrum of compound **2** revealed signals at 2.28, 2.51 and 5.27 ppm due to two methyl groups and amide-NH proton, respectively, in addition to an aromatic multiplet in the region 7.33–7.52 ppm. The analysis of the ^{13}C NMR spectrum revealed that the signal of the CN group appeared at δ 111.6 ppm and C═O group at 170.9 ppm. The intermediate **2** undergoes an intramolecular cyclization in the presence of piperidine in ethanol to yield pyrazolopyrimidinone **3** (Scheme 1) (Ali, 2009). The IR spectrum of compound **3** revealed the presence of characteristic absorption bands at 1680 and 3240 cm^{-1} assignable to carbonyl and NH functions, respectively, beside the disappearance of the CN group absorption band. The disappearance of the cyano signal from the ^{13}C NMR spectrum of compound **3** is in favor of an intramolecular cyclization. Also, the structure of compound **3** was supported by its ES-HRMS which showed a pseudo molecular ion peak $[M+H]^+$ at *m/z* 241.1083.

First, the required dipolarophiles **4** and **5** were, respectively, prepared by *N*-allylation and *N*-propargylation (Mabrour et al., 2007) of pyrazolopyrimidinone **3** (Scheme 1). Indeed, in our investigation, dimethylformamide was found to be an excellent solvent for the reaction of allyl and propargyl bromide with pyrazolopyrimidinone **3**, in the presence of NaH. DMF is especially effective in this reaction for weakening the bromine–carbon bond. The *N*-allyl and *N*-propargyl pyrazolopyrimidinones **4** and **5** were obtained in 78% and 80% yield, respectively. So the reaction is complete after 1 h at room temperature.

Dipolarophiles **4** and **5** were then treated with various arylnitrile oxides generated *in situ* from aromatic oxime (Saad et al., 2004; Tronchet et al., 1970) precursors under conventional conditions furnished the desired isoxazolines **6a–f** or isoxazoles **7a–g**, respectively, in high yields (75–80%) (Scheme 2).

The structures of these compounds were confirmed according to their spectral data, where the IR spectra of compounds **6a–f** indicated the existence of the isoxazoline C═N group at ν_{max} = 1630–1640 cm^{-1}. The ^{1}H NMR spectra of **6a–f** shows duplication of most signals allowed to conclude the formation of two diastereoisomers due to the presence of two asymmetric centers, the alkylated nitrogen of pyrazolopyrimidinone and the stereogenic center of isoxazoline. Attempts to separate these diastereoisomers by chromatography were not successful. In the ^{1}H NMR spectrum of compound **6c** as an example we observed two singlets at 2.19 and 2.50 ppm attributable to the methyl group protons $(CH_3)_{-8}$ while the two singlets of the other methyl group protons $(CH_3)_{-9}$ resonate at 2.04 and 2.45 ppm. The same spectrum showed a multiplet centered at 4.91 ppm attributable to the CH stereogenic center and two doublets of doublets at 3.17 ppm (J = 16.8 Hz, 7.2 Hz) and at 3.43 ppm (J = 16.8 Hz, 10.5 Hz) corresponding to the methylenic protons $H_{4'a/b}$ of the first diastereoisomer noted A and two other doublets of doublets at 3.20 (J = 16.8 Hz, 9.0 Hz) and 3.46 ppm (J = 16.8 Hz, 10.2 Hz) attributable to the same protons of the second diastereoisomer B. The *N*—CH_2 protons of the mixture of the two diastereoisomers appeared as for doublets of doublets at 2.84 ppm (J = 14.1 Hz, 7.5 Hz) and at 4.23 ppm (J = 14.1 Hz, 5.1 Hz), relative to the diastereoisomer A or B and at 3.55 ppm (J = 14.7 Hz, 3.9 Hz) and at 3.99 ppm (J = 14.7 Hz, 6.0 Hz) corresponding to the diastereoisomer B or A. The aromatic protons in both diastereoisomers A and B exhibited a multiplet at 7.03–7.54 ppm. ^{13}C NMR spectrum of **6c** exhibited a signal at 50.2 ppm corresponding to *N*—CH_2 carbon and two signals at 39.1 ppm and 78.6 ppm relative to the isoxazoline carbons $C_{4'}$ and $C_{5'}$, respectively. The C═N and carbonyl carbons $C_{3'}$ and C_4 resonated at 170.2 and 169.7 ppm, respectively. The structures of compounds **6a–f** were further confirmed by mass spectrometry.

The regioselectivity of this cycloaddition reaction generally leads to a mixture of 1,4 and 1,5-regioisomers (Kiss et al.,

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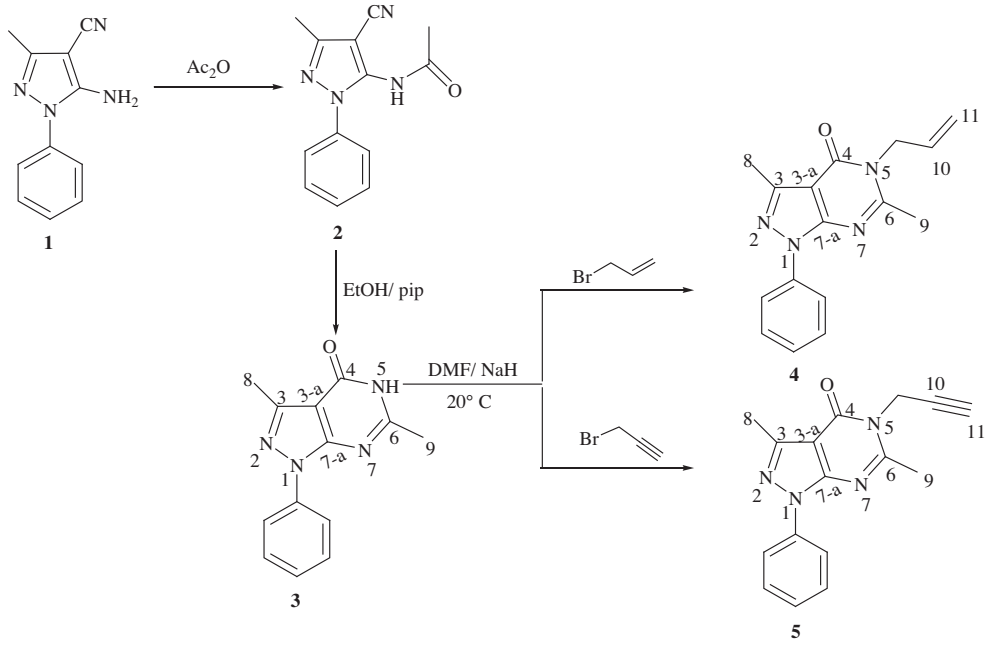
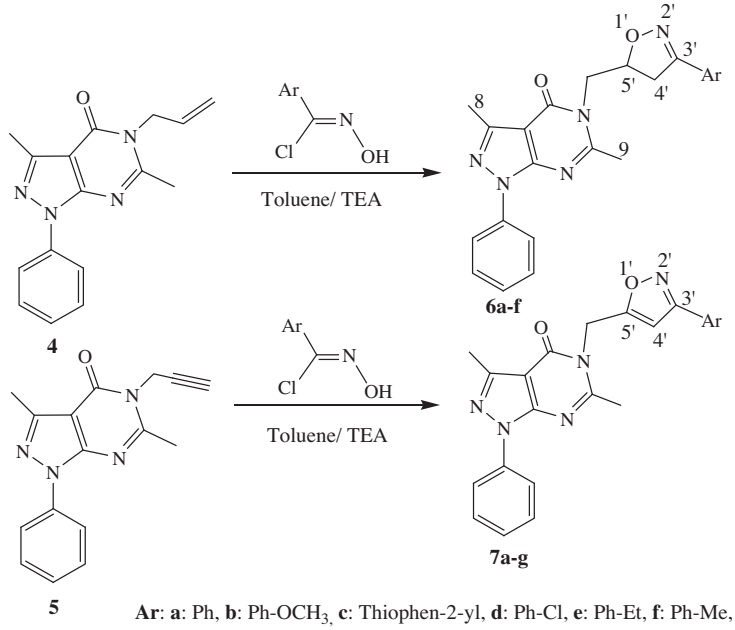


Scheme 1 Synthetic route of compounds **2–5**.



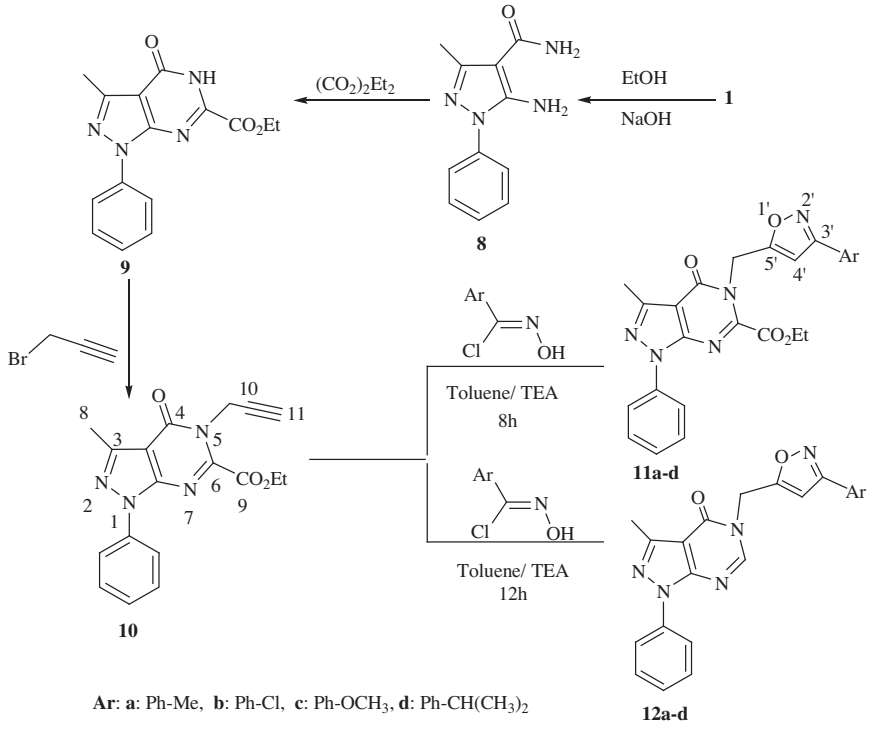
Ar: **a**: Ph, **b**: Ph-OCH_3, **c**: Thiophen-2-yl, **d**: Ph-Cl, **e**: Ph-Et, **f**: Ph-Me, **g**: Ph-$CH(CH_3)_2$

Scheme 2 Synthetic route of isoxazolines and isoxazoles **6a–f** and **7a–g**.

2009). Although, in this study the novel 1,2,4-isoxazoline derivatives **6a–f** were formed as unique products, indicating the regiospecificity of the reaction. Indeed, the nonformation of the other 1,5-regioisomer was proven by the absence of any duplication of signals on the spectra of ^1H and ^{13}C NMR of the reaction crude and it may be explained by a possible steric crowding factor.

Similarly, the IR spectrum of compound **7c** showed an absorption at $\nu_{max} = 1611\ cm^{-1}$ due to the isoxazole C═N bond. The ^1H NMR spectrum of **7c** showed two doublets at 4.37 ppm ($J = 15.9$ Hz) and at 5.08 ppm ($J = 15.9$ Hz) attributed to the N—CH_2 protons. The $C_{4'\text{-H}}$ isoxazole proton resonated as a singlet at 6.53 ppm and all the aromatic protons as a multiplet at 7.09–7.50 ppm. The ^{13}C NMR spectrum showed a signal at 42.5 ppm for the N—CH_2 carbon and two signals at 102.5 ppm and 160.7 ppm for the two characteristic isoxazole carbons $C_{4'}$ and $C_{5'}$, respectively. The C═N and carbonyl carbons $C_{3'}$ and C_4 resonated at 152.4 ppm and 169.8 ppm, respectively. Mass spectrometry is also in accordance with the proposed structure for compounds **7a–g**.

As shown in Scheme 3, treatment of the aminopyrazole **1** in refluxing with ethanol in the presence of sodium hydroxide



Scheme 3 Synthetic route of compounds **8–10**, **11a–d** and **12a–d**.

afforded the corresponding carboxamide **8** with a yield of 80%. Then, **8** were converted to the pyrazolopyrimidinone **9** with neat diethyl oxalate under reflux. In order to access to new isoxazole pyrazolopyrimidinones, the *N*-propargylation of **9** afforded the dipolarophile **10** which was then subjected to a reaction of *1,3*-dipolar cycloaddition. The cycloaddition reaction of arylnitrile oxides and dipolarophile **10**, under conventional conditions by refluxing in toluene in the presence of a catalytic amount of triethylamine for 8 h provided cycloadducts **11a–d** in excellent to moderate yields (80–65%).

The structure of compound **10** was established on the basis of its spectral data. The IR spectrum showed absorption bands at 2100 cm^{-1} (C≡C), at 1670 cm^{-1} (N—C═O) and at 1720 cm^{-1} (C═O). The ^1H NMR spectrum showed the absence of the signal related to the mobile proton (—NH—) and the observation of a doublet at 5.12 ppm (J = 2.4 Hz) relative to the methylene group (N—CH_2), a triplet at 2.33 ppm (J = 2.4 Hz) attributable to the acetylenic proton (C≡C—H) and the presence of signals relative to the ester group. The cycloadducts **11a–d** were obtained and their structures were confirmed through spectral analysis where the IR spectrum of compound **11b** as an example indicated the existence of the isoxazole C═N group at ν_{max} = 1620 cm^{-1}. The ^1H NMR spectrum of **11b** showed the disappearance of the C≡C—H characteristic signal, the appearance of a new singlet at 6.60 ppm characteristic of the $C_{4'\text{-}H}$ isoxazole proton and the presence of the specific signals of the ester group. The same reaction of the dipolarophile **10** with the arylnitrile oxide maintained for 12 h, afforded the deethoxycarbonylated cycloadducts **12**. The ^1H NMR spectra showed the disappearance of the characteristic signals of the ester group at position 6 indicating that pyrazolopyrimidinones evolved into a carboxylic acid form followed by a decarboxylation.

3. Conclusion

In conclusion, this work reports the synthesis of *N*-allyl or propargyl pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones **4**, **5** and **10**, in three steps starting from the key intermediate the aminopyrazoles **1**. In the second part we have described the successful access to a new pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones derivatives, **6**, **7**, **11** and **12**, incorporating the isoxazoline or isoxazole moiety in good yields *via 1,3*-dipolar cycloaddition of some arylnitrile oxides and starting precursors **4**, **5** and **10**.

4. Experimental section

All melting points were determined on a Kofler-type microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer Fourier transform FT-IR spectrophotometer (4000–400 cm^{-1}) using KBr pellets or CCl_4 solution. ^1H NMR and ^{13}C NMR spectra were recorded at room temperature (rt) in $CDCl_3$ and dimethylsulfoxide (DMSO-d_6) at 300 MHz and at 75 MHz, respectively, using residual nondeuterated solvent peaks as internal reference. Coupling constants are given in Hz. HRMS spectra were acquired with an electrospray-time-of-flight (ESI-TOF, LCT Premier XE, Waters) mass spectrometer in the positive ion mode.

4.1. General procedure for the preparation of 3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one 3

Solution of **1** (0.01 mol), in acetic anhydride (20 mL) was refluxed for 6 h. The reaction mixture was evaporated under vacuum and the obtained product was crystallized from dichloromethane to give **2**. A few drops of piperidine were

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added to an ethanolic solution (25 mL) of compound **2** and the reaction mixture was refluxed for 4 h. The solid product that formed was filtered off, dried, and purified by recrystallization in EtOH to afford compound **3**.

White crystals, yield 78%, mp: 277–279 °C; IR (KBr, cm^{-1}): 3240 (NH), 1680 (C═O). ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, H_9), 2.39 (s, 3H, H_8), 7.40–7.51 (m, 5H, Ar—H), 8.14 (s, 1H, —NH—). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0 (C_8), 22.4 (C_9), 113.1 ($C_{3\text{-a}}$), 123.8, 127.8, 130.7, 137.1 (C_{arom}), 139.7 ($C_{7\text{-a}}$), 151.9 (C_3), 160.2 (C_6), 169.0 (C_4). HRMS $[M+H]^+$ calcd for $(C_{13}H_{13}N_4O)^+$ 241.1083, found 241.1089.

*4.2. General procedure for N-allylation and N-propargylation of 3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-ones **4** and **5***

The pyrazolopyrimidinone **3** (0.4 g) was added in portions to a stirred suspension of NaH (0.1 g) in dry DMF (15 mL) at 20 °C. After the addition was over, the mixture was stirred at 20 °C for 30 min. A solution of allyl bromide/propargyl bromide (2 mL) in DMF (5 mL) was added dropwise to the mixture at 20 °C and the stirring was continued for 30 min. The whole reaction mixture was poured into water (100 mL) and extracted with EtOAc. The organic layer was dried and concentrated in vacuo affording compounds **4** and **5**, respectively.

*4.2.1. 5-Allyl-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**4**)*

Yellowish liquid, yield 75%, IR (CCl_4, cm^{-1}): 1680 (C═O), 1675 (C═C), 3094 (C—H allyl). ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (s, 3H, H_9), 2.39 (s, 3H, H_8), 3.37 (dd, 1H, *N*—CH_2, J = 7.2 Hz, J = 14.7 Hz), 4.57 (dd, 1H, *N*—CH_2, J = 7.2 Hz, J = 14.7 Hz), 4.98–5.11 (m, —CH═$\underline{CH_2}$), 5.67 (m, —$\underline{CH}$═CH_2), 7.26–7.48 (m, 5H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2 (C_8), 21.9 (C_9), 50.5 (*N*—CH_2), 112.3 ($C_{3\text{-a}}$), 120.0 (—CH═$\underline{CH_2}$), 130.9 ($\underline{CH}$═CH_2), 120.5–137.1 (C_{arom}), 140.0 ($C_{7\text{-a}}$), 144.2 (C_3), 152.2 (C_6), 169.3 (C_4). HRMS $[M+H]^+$ calcd for $(C_{16}H_{17}N_4O)^+$ 281.1399, found 281.1402.

*4.2.2. 3,6-Dimethyl-1-phenyl-5-(prop-2-ynyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**5**)*

Yellowish liquid, yield 80%; IR (CCl_4, cm^{-1}): 1675 (C═O), 3370 (CH propynyl). ^1H NMR (300 MHz, $CDCl_3$): δ 1.93 (s, 3H, H_9), 2.27 (t, 1H, —C≡C—H, J = 2.4 Hz), 2.84 (s, 3H, H_8), 4.10–4.16 (dd, *N*—CH_2, J = 2.4 Hz, J = 17.4 Hz), 4.58–4.64 (dd, *N*—CH_2, J = 2.4 Hz, J = 17.4 Hz), 7.31–7.47 (m, 5H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.30 (C_8), 22.2 (C_9), 37.1 (*N*—CH_2), 67.9 (C_{11}), 92.8 (C_{10}), 111.9 ($C_{3\text{-a}}$), 123.5–129.8 (C_{arom}), 137.0 ($C_{7\text{-a}}$), 143.2 (C_3), 152.3 (C_6), 168.8 (C_4). HRMS $[M+H]^+$ calcd for $(C_{16}H_{15}N_4O)^+$ 279.1246, found 279.1247.

*4.3. General procedure for the synthesis of isoxazolines **6a–f** and isoxazoles **7a–g***

A mixture of dipolarophile **4** or **5** (3 eq) and arylnitrile oxide (1 eq) was dissolved in toluene in the presence of a catalytic amount of triethylamine, the solution was then refluxed for 8 h. The reaction was monitored with TLC after the completion of the reaction, the reaction mixture concentrated and cooled. The product formed in each case was purified by column chromatography using 9:1 mixture of chloroform and ethylacetate to yield compounds **6** or **7**.

*4.3.1. 3,6-Dimethyl-1-phenyl-5-((3-pheny-4,5-dihydroisxazol-5-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**6a**)*

White crystals, yield 65%, mp: 125–127 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1635 (isoxazoline C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.04–2.45 (2s, 3H, H_9), 2.19–2.50 (2s, 3H, H_8), 2.81 (dd, *N*—$CH_{2A/B}$, J = 14.1 Hz, 7.5 Hz), 4.21 (dd, *N*—$CH_{2A/B}$, J = 14.1 Hz, 5.1 Hz), 3.54 (dd, *N*—$CH_{2A/B}$, J = 14.7 Hz, 4.0 Hz), 3.97 (dd, *N*—$CH_{2A/B}$, J = 14.7 Hz, 6.0 Hz), 3.15 (dd, C4′HaHb/A, J = 16.8 Hz, 7.2 Hz), 3.42 (dd, C4′HaHb/A, J = 16.8 Hz, 10.5 Hz), 3.21 (dd, C4′HaHb/B, J = 16.8 Hz, 9.0 Hz), 3.45 (dd, C4′HaHb/B, J = 16.8 Hz, 10.2 Hz), 4.90 (m, 1H, $H_{5'}$), 7.26–7.66 (m, 20H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6 (C_8), 21.5 (C_9), 38.1($C_{4'}$), 49.8 (*N*–CH_2), 78.5 ($C_{5'}$), 111.5 ($C_{3\text{-a}}$), 122.8–136.4 (C_{arom}), 140.3 ($C_{7\text{-a}}$), 143.4 (C_3), 152.3 (C_6), 166($C_{3'}$), 169.4 (C_4). HRMS $[M+H]^+$ calcd for $(C_{23}H_{22}N_5O_2)^+$ 400.1716, found 400.1729.

*4.3.2. 5-((3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl)methyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**6b**)*

White crystals, yield 75%, mp: 128–130 °C; IR (KBr, cm^{-1}): 1679 (C═O), 1630 (isoxazoline C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.04–2.44 (2s, 3H, H_9), 2.18–2.50 (2s, 3H, H_8), 2.81 (dd, *N*—$CH_{2A/B}$, J = 14.1 Hz, 7.5 Hz), 4.24 (dd, *N*—$CH_{2A/B}$, J = 14.1 Hz, 5.1 Hz), 3.52 (dd, *N*—$CH_{2A/B}$, J = 14.7 Hz, 3.9 Hz), 3.91 (dd, *N*—$CH_{2A/B}$, J = 14.7 Hz, 6.0 Hz), 3.84 (2s, 3H, —OCH_3), 3.06 (dd, C4′HaHb/A, J = 16.8 Hz, 7.2 Hz), 3.41 (dd, C4′HaHb/A, J = 16.8 Hz, 10.5 Hz), 3.11 (dd, C4′HaHb/B, J = 16.8 Hz, 9.0 Hz), 3.47 (dd, C4′HaHb/B, J = 16.8 Hz, 10.2 Hz), 4.88 (m, 1H, $H_{5'}$), 6.87–7.60 (m, 18H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7 (C_8), 21.5 (C_9), 38.6 ($C_{4'}$), 50.3 (*N*—CH_2), 54.8 (—O$\underline{CH_3}$), 78.1 ($C_{5'}$), 111.8 ($C_{3\text{-a}}$), 122.8–158.3 (C_{arom}), 141.6 ($C_{7\text{-a}}$), 144.7 (C_3), 152.3 (C_6), 160.6($C_{3'}$), 169.6 (C_4). HRMS $[M+H]^+$ calcd for $(C_{24}H_{24}N_5O_3)^+$ 430.1860, found 430.1879.

*4.3.3. 3,6-Dimethyl-1-phenyl-5-((3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**6c**)*

White crystals, yield 75%, mp: 112–114 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1635 (isoxazoline C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.04–2.45 (2s, 3H, H_9), 2.19–2.50 (2s, 3H, H_8), 2.84 (dd, *N*—$CH_{2A/B}$, J = 14.1 Hz, 7.5 Hz), 4.23 (dd, *N*—$CH_{2A/B}$, J = 14.1 Hz, 5.1 Hz), 3.55 (dd, *N*—$CH_{2A/B}$, J = 14.7 Hz, 3.9 Hz), 3.99 (dd, *N*—$CH_{2A/B}$, J = 14.7 Hz, 6.0 Hz), 3.17 (dd, C4′HaHb/A, J = 16.8 Hz, 7.2 Hz), 3.43 (dd, C4′HaHb/A, J = 16.8 Hz, 10.5 Hz), 3.20 (dd, C4′HaHb/B, J = 16.8 Hz, 9.0 Hz), 3.46 (dd, C4′HaHb/B, J = 16.8 Hz, 10.2 Hz), 4.91 (m, 1H, $H_{5'}$), 7.03–7.54 (m, 16H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (C_8), 21.5 (C_9), 39.1 ($C_{4'}$), 50.2 (*N*—CH_2), 78.6 ($C_{5'}$), 111.7 ($C_{3\text{-a}}$), 122.8–151.7 (C_{arom}), 143.6 ($C_{7\text{-a}}$), 144.6 (C_3), 152.3 (C_6), 169.7 (C_4), 170.2 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{21}H_{20}N_5O_2S)^+$ 406.1338, found 406.1338.

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*4.3.4. 5-((3-(4-Chlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**6d**)*

White crystals, yield 73%, mp: 136–138 °C; IR (KBr, cm^{-1}): 1675 (C═O), 1640 (isoxazoline C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.91–2.37 (2s, 3H, H_9), 2.1–2.43 (2s, 3H, H_8), 2.75 (dd, *N*—$CH_{2A/B}$, *J* = 14.1 Hz, 7.5 Hz), 4.18 (dd, N—$CH_{2A/B}$, *J* = 14.1 Hz, 5.1 Hz), 3.40 (dd, *N*—$CH_{2A/B}$, *J* = 14.7 Hz, 4.0 Hz), 3.96 (dd, N—$CH_{2A/B}$, *J* = 14.7 Hz, 6.0 Hz), 3.04 (dd, C4′HaHb/A, *J* = 16.8 Hz, 7.2 Hz), 3.40 (dd, C4′HaHb/A, *J* = 16.8 Hz, 10.5 Hz), 3.12 (dd, C4′HaHb/B, *J* = 16.8 Hz, 9.0 Hz), 3.44 (dd, C4′HaHb/B, *J* = 16.8 Hz, 10.2 Hz), 4.83 (m, 1H, $H_{5'}$), 7.21–7.52 (m, 18H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (C_8), 22.06 (C_9), 37.5 ($C_{4'}$), 50.2 (*N*—CH_2), 79.2 ($C_{5'}$), 111.3 ($C_{3\text{-a}}$), 122.8–136.3 (C_{arom}), 143.6 ($C_{7\text{-a}}$), 144.6 (C_3), 155.3 (C_6), 168.7 ($C_{3'}$), 170.6 (C_4). HRMS $[M+H]^+$ calcd for $(C_{23}H_{21}ClN_5O_2)^+$ 434.1379, found 434.1384.

*4.3.5. 5-((3-(4-Ethylphenyl)-4,5-dihydroisoxazol-5-yl)methyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**6e**)*

White crystals, yield 70%, mp: 128–130 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1637 (isoxazoline C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.17–1.27 (2t, 3H, *J* = 7.2 Hz, —CH_2—$\underline{CH_3}$), 1.95–2.36 (2s, 3H, H_9), 2.41–2.59 (2q, 2H, *J* = 7.2 Hz, —$\underline{CH_2}$—CH_3), 2.09–2.44 (2s, 3H, H_8), 2.74 (dd, *N*—$CH_{2A/B}$, *J* = 14.1 Hz, 7.5 Hz), 4.15 (dd, *N*—$CH_{2A/B}$, *J* = 14.1 Hz, 5.1 Hz), 3.37 (dd, *N*—$CH_{2A/B}$, *J* = 14.7 Hz, 3.9 Hz), 3.89 (dd, *N*—$CH_{2A/B}$, *J* = 14.7 Hz, 6.0 Hz), 3.01 (dd, C4′HaHb/A, *J* = 16.8 Hz, 7.2 Hz), 3.28 (dd, C4′HaHb/A, *J* = 16.8 Hz, 10.5 Hz), 3.09 (dd, C4′HaHb/B, *J* = 16.8 Hz, 9.0 Hz), 3.39 (dd, C4′HaHb/B, *J* = 16.8 Hz, 10.2 Hz), 4.80 (m, 1H, $H_{5'}$), 7.06–7.69 (m, 18H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2 (C_8), 15.2 (—CH_2—$\underline{CH_3}$), 22.0 (C_9), 28.7 (—$\underline{CH_2}$—CH_3), 38.0 ($C_{4'}$), 50.4 (*N*—CH_2), 78.2 ($C_{5'}$), 112.3 ($C_{3\text{-a}}$), 120.8–137.3 (C_{arom}), 144.2 ($C_{7\text{-a}}$), 146.6 (C_3), 152.1 (C_6), 157.0 ($C_{3'}$), 170.5 (C_4). HRMS $[M+H]^+$ calcd for $(C_{25}H_{26}N_5O_2)^+$ 428.2079, found 428.2087.

*4.3.6. 3,6-Dimethyl-1-phenyl-5-((3-p-toly-4,5-dihydroisoxazol-5-yl)methyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**6f**)*

White crystals, yield 75%, mp: 132–134 °C; IR (KBr, cm^{-1}): 1678 (C═O), 1635 (isoxazoline C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.97–2.45 (2s, 3H, H_9), 2.37–2.40 (2s, 3H, CH_3), 2.19–2.51 (2s, 3H, H_8), 2.82 (dd, *N*—$CH_{2A/B}$, *J* = 14.1 Hz, 7.5 Hz), 4.24 (dd, *N*—$CH_{2A/B}$, *J* = 14.1 Hz, 5.1 Hz), 3.55 (dd, *N*—$CH_{2A/B}$, *J* = 14.7 Hz, 3.9 Hz), 4.00 (dd, *N*—$CH_{2A/B}$, *J* = 14.7 Hz, 6.0 Hz), 3.10 (dd, C4′HaHb/A, *J* = 16.8 Hz, 7.2 Hz), 3.40 (dd, C4′HaHb/A, *J* = 16.8 Hz,7.2 Hz), 3.15 (dd, C4′HaHb/B, *J* = 16.8 Hz,7.2 Hz), 3.44 (dd, C4′HaHb/B, *J* = 16.8 Hz,7.2 Hz), 4.91 (m, 1H, $H_{5'}$), 7.10–7.63 (m, 18H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (C_8), 21.0 (CH_3), 21.5 (C_9), 38.5 ($C_{4'}$), 50.3 (*N*—CH_2), 78.2 ($C_{5'}$), 111.8 ($C_{3\text{-a}}$), 122.8–140.1 (C_{arom}), 144.7 ($C_{7\text{-a}}$), 151.7 (C_3), 156.5 (C_6), 162.7 ($C_{3'}$), 170.1 (C_4). HRMS $[M+H]^+$ calcd for $(C_{24}H_{24}N_5O_2)^+$ 414.1930, found 414.1930.

*4.3.7. 3,6-Dimethyl-1-phenyl-5-((3-phenylisxazol-5-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**7a**)*

White crystals, yield 70%, mp: 122–124 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1611 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, H_9), 2.46 (s, 3H, H_8), 4.40 (d, *N*—CH_2, *J* = 15.6 Hz), 5.09 (d, *N*—CH_2, *J* = 15.6 Hz), 6.55 (s, 1H, $H_{4'}$), 7.26–7.66 (m, 10H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2 (C_8), 21.8 (C_9), 42.1 (*N*—CH_2), 102.4 ($C_{4'}$), 111.6 ($C_{3\text{-a}}$), 123.5–136.7 (C_{arom}), 140.3 ($C_{7\text{-a}}$), 143.4 (C_3), 151.2 (C_6), 162.7 ($C_{5'}$), 166 (C_4), 169.4 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{23}H_{20}N_5O_2)^+$ 398.1172, found 398.1179.

*4.3.8. 5-((3-(4-Methoxyphenyl)isoxazol-5-yl)methyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**7b**)*

White crystals, yield 75%, mp: 124–126 °C; IR (KBr, cm^{-1}): 1679 (C═O), 1614 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H, H_9), 2.41 (s, 3H, H_8), 3.41 (s, 3H, —O—CH_3), 4.32 (d, *N*—CH_2, *J* = 15.6 Hz), 5.09 (d, *N*—CH_2, *J* = 15.6 Hz), 6.50 (s, 1H, $H_{4'}$), 7.24–7.61 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3 (C_8), 21.7 (C_9), 42.1 (*N*—CH_2), 54.8 (—OCH_3), 101.1 ($C_{4'}$), 111.8 ($C_{3\text{-a}}$), 123.5–160.7 (C_{arom}), 142.2 ($C_{7\text{-a}}$), 143.7 (C_3), 151.2 (C_6), 162.1 ($C_{5'}$), 168.7 (C_4), 169.5 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{24}H_{22}N_5O_3)^+$ 428.1672, found 428.1678.

*4.3.9. 3,6-Dimethyl-1-phenyl-5-((3-(thiophen-2-yl)isoxazol-5-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**7c**)*

White crystals, yield 80%, mp: 110–112 °C; IR (KBr, cm^{-1}): 1675 (C═O), 1611 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H, H_9), 2.41 (s, 3H, H_8), 4.37 (d, *N*—CH_2, *J* = 15.6 Hz), 5.08 (d, *N*—CH_2, *J* = 15.6 Hz), 6.53 (s, 1H, $H_{4'}$), 7.09–7.50 (m, 8H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.27 (C_8), 22.1 (C_9), 42.5 (*N*—CH_2), 102.5 ($C_{4'}$), 111.5 ($C_{3\text{-a}}$), 123.1–136.7 (C_{arom}), 143.2 ($C_{7\text{-a}}$), 152.1 (C_3), 152.4 ($C_{3'}$), 158.1 (C_6), 160.7($C_{5'}$), 169.8 (C_4). HRMS $[M+H]^+$ calcd for $(C_{21}H_{18}N_5O_2S)^+$ 404.1181, found 404.1195.

*4.3.10. 5-((3-(4-Chlorophenyl)isoxazol-5-yl)methyl)-3, 6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**7d**)*

White crystals, yield 78%, mp: 138–140 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1613 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, H_9), 2.45 (s, 3H, H_8), 4.33 (d, *N*—CH_2, *J* = 15.6 Hz), 5.14 (d, *N*—CH_2, *J* = 15.6 Hz), 6.58 (s, 1H, $H_{4'}$), 7.34–7.71 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.23 (C_8), 21.8 (C_9), 42.6 (*N*—CH_2), 102.3 ($C_{4'}$), 111.8 ($C_{3\text{-a}}$), 123.1–136.8 (C_{arom}), 143.3 ($C_{7\text{-a}}$), 147.1 (C_3), 152.4 (C_6), 161.8 ($C_{5'}$), 166.6 (C_4), 169.5 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{23}H_{19}ClN_5O_2)^+$ 432.1227, found 432.1231.

*4.3.11. 5-((3-(4-Ethylphenyl)isoxazol-5-yl)methyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**7e**)*

White crystals, yield 70%, mp: 144–146 °C; IR (KBr, cm^{-1}): 1675 (C═O), 1614 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, 3H, *J* = 7.2 Hz, —CH_2—$\underline{CH_3}$), 2.10 (s, 3H, H_9), 2.44 (q, 2H, *J* = 7.2 Hz, —$\underline{CH_2}$—CH_3), 2.51 (s, 3H, H_8), 4.30 (d, *N*—CH_2, *J* = 15.6 Hz), 5.01 (d, *N*—CH_2, *J* = 15.6 Hz), 6.52 (s, 1H, $H_{4'}$), 7.21–7.77 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3 (C_8), 13.8 (—CH_2—$\underline{CH_3}$), 22.1 (C_9), 31.8 (—$\underline{CH_2}$—CH_3), 41.8 (*N*—CH_2), 100.1 ($C_{4'}$), 111.1 ($C_{3\text{-a}}$), 123.5–137.7 (C_{arom}), 142.1 ($C_{7\text{-a}}$), 143.1 (C_3),

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151.1 (C_6), 162.2 ($C_{5'}$), 168.6 (C_4), 169.4 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{25}H_{24}N_5O_2)^+$ 426.1885, found 426.1885.

4.3.12. 3,6-Dimethyl-1-phenyl-5-((3-p-tolylisxazol-5-yl)methyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (7f)

White crystals, yield 75%, mp: 140–142 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1612 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, H_9), 2.40–2.46 (s, 2CH_3, H_8 and Ph-CH_3), 4.40 (d, *N*—CH_2, J = 15.6 Hz), 5.12 (d, *N*—CH_2, J = 15.6 Hz), 6.57 (s, 1H, $H_{4'}$), 7.34–7.71 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.22 (C_8), 21.4 (C_9), 21.8 (Ph-CH_3), 42.5 (*N*—CH_2), 102.3 ($C_{4'}$), 111.6 ($C_{3\text{-}a}$), 123.5–136.8 (C_{arom}), 140.3 ($C_{7\text{-}a}$), 144.1 (C_3), 152.4 (C_6), 162.7 ($C_{5'}$), 166.0 (C_4), 169.4 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{24}H_{22}N_5O_2)^+$ 412.1774, found 412.1783.

4.3.13. 5-((3-(4-Isopropylphenyl)isoxazol-5-yl)methyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (7g)

White crystals, yield 80%, mp: 137–139° C; IR (KBr, cm^{-1}): 1680 (C═O), 1611 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.16–120 (s, 6H, —CH—($\underline{CH_3}$)$_2$), 2.04 (s, 3H, H_9), 2.41 (s, 3H, H_8), 2.86 (m, 1H, —$\underline{CH}$—(CH_3)$_2$), 4.30 (d, *N*—CH_2, J = 15.9 Hz), 5.01 (d, *N*—CH_2, J = 15.9 Hz), 6.49 (s, 1H, $H_{4'}$), 7.18–7.61 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.22 (C_8), 21.9 (C_9), 23.8 (—CH—($\underline{CH_3}$)$_2$), 34.0 (—$\underline{CH}$—(CH_3)$_2$), 42.5 (*N*—CH_2), 102.4 ($C_{4'}$), 111.8 ($C_{3\text{-}a}$), 123.5–143.4 (C_{arom}), 151.2 ($C_{7\text{-}a}$), 152.3 (C_3), 162.7 (C_6), 166.0 ($C_{5'}$), 168.8 (C_4), 169.4 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{26}H_{26}N_5O_2)^+$ 440.2087, found 440.2101.

4.4. General procedure for the preparation of 5-Amino-3-methyl-1-phenyl-1H-pyrazole-4-carboxamide 8

To a solution of **1** (1.22 g, 11.3 mmol) in ethanol (10.0 mL) was added dropwise a solution of 33.3% sodium hydroxide (12.0 mL). The mixture was then heated under reflux for 6 h. After cooling to room temperature, the reaction mixture was concentrated under vacuum and 6 M HCl solutions was added until pH 4. After cooling in ice water for 4 h, the precipitated solid was filtered, washed with water and dried to yield compound **8**.

Yellowish solid, yield 80%, mp: 260–262 °C; IR (KBr, cm^{-1}): 1675 (C═O), 3483–3219 (NH_2). ^1H NMR (300 MHz, DMSO-d_6): δ 3.51 (s, 3H, CH_3), 6.41 (s, 2H, NH_2), 6.71 (s, 2H, NH_2), 7.33–7.56 (m, 5H, Ar—H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.4 (CH_3), 96.2 (C_4), 122.9–138.1 (C_{arom}), 146.2 (C_3), 150.3 (C_5), 166.9 (C═O).

4.5. General procedure for the preparation of ethyl 3-methyl-4-oxo-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylate 9

A mixture of **8** (2.50 g, 12.40 mmol) and diethyl oxalate (8.2 mL) was refluxed for 5 h and the reaction mixture was allowed to cool to room temperature. The precipitate was collected, washed with petroleum ether and dried to give compound **9**.

White solid, yield 60%, mp: 132–134 °C; IR (KBr, cm^{-1}): 1680 (C═O), 3195 (NH_2). ^1H NMR (300 MHz, $CDCl_3$): δ 1.47 (t, 3H, J = 6.9 Hz, —O—CH_2—$\underline{CH_3}$), 2.70 (s, 3H, H_8), 4.53 (q, 2H, J = 6.9 Hz, —O—$\underline{CH_2}$—CH_3), 7.26–8.07 (m, 5H, Ar—H), 10.50 (s, 1H, —NH—). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0 (—O—CH_2—$\underline{CH_3}$), 13.5 (CH_3), 63.5 (—O—$\underline{CH_2}$—CH_3), 106.5 ($C_{3\text{-}a}$), 121.5–137.7 (C_{arom}), 146.9 ($C_{7\text{-}a}$), 150.8 (C_3), 157.1 (C_6), 159.4 (C═O). HRMS $[M+H]^+$ calcd for $(C_{15}H_{15}N_4O_3)^+$ 299.1063, found 299.1066.

4.6. General procedure for the preparation of ethyl 3-methyl-4-oxo-1-phenyl-5-(prop-2-ynyl)-4, 5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylate 10

The pyrazolopyrimidinone **9** (0.4 g) was added in portions to a stirred suspension of NaH (0.1 g) in dry DMF (15 mL) at 0 °C. After the addition was over, the mixture was stirred at 0 °C for 30 min. A solution of propargyl bromide (2 mL) in DMF (5 mL) was added dropwise to the mixture at 20 °C and the stirring was continued for 30 min. The whole reaction mixture was poured into water (100 mL) and extracted with EtOAc. The organic layer was dried and concentrated in *vacuo* affording compound **10**.

Yellowish liquid, yield 78%; IR (CCl_4, cm^{-1}): 2100 (C≡C), 1720 (C═O), 1670 (N—C═O), ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (t, 3H, J = 7.2 Hz, —CH_2—$\underline{CH_3}$), 2.33 (t, 1H, —C≡C—H, J = 2.4 Hz), 2.76 (s, 3H, H_8), 4.50 (q, 2H, J = 6.9 Hz, —$\underline{CH_2}$—CH_3), 4.12 (d, *N*—CH_2, J = 2.4 Hz), 7.33–8.05 (m, 5H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.01 (—CH_2—$\underline{CH_3}$), 13.4 (C_8), 37.8 (*N*—CH_2), 63.0 (—CH_2—$\underline{CH_3}$), 72.6 (C_{10}), 78.1 (C_{11}), 104.7 ($C_{3\text{-}a}$), 121.4–137.6 (C_{arom}), 147.1 ($C_{7\text{-}a}$), 148.9 (C_3), 156.3 (C_9), 160.4 (C_4). HRMS $[M+H]^+$ calcd for $(C_{18}H_{17}N_4O_3)^+$ 337.1250, found 337.1256.

4.7. General procedure for the preparation of cycloadducts 11a–d and 12a–d

A mixture of dipolarophile **10** (1 eq) with arylnitrile oxide (1 eq) in toluene in the presence of a catalytic amount of triethylamine was refluxed for 8 h. The reaction was monitored with TLC after the completion of the reaction, the reaction mixture concentrated and cooled. The products **11** formed were purified by column chromatography using 8.5:1.5 mixtures of chloroform and ethylacetate. The above same reaction maintained for 12 h afforded the deethoxycarbonylated cycloadducts **12**.

4.7.1. Ethyl 3-methyl-4-oxo-1-phenyl-5-((3-p-tolylisoxazol-5-yl)methyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylate (11a)

White crystals, yield 78%, mp: 143–145 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1615 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, 3H, J = 7.2 Hz, —O—CH_2—$\underline{CH_3}$), 2.28 (s, 3H, CH_3), 2.73 (s, 3H, H_8), 4.50 (q, 2H, J = 6.9 Hz, —O—$\underline{CH_2}$—CH_3), 5.63 (s, 2H, *N*—CH_2), 6.58 (s, 1H, $H_{4'}$), 7.30–8.01 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.01 (—O—CH_2—$\underline{CH_3}$), 13.8 (C_8), 37.8 (*N*—CH_2), 63.0 (O—CH_2—$\underline{CH_3}$), 100.1 ($C_{4'}$), 111.2 ($C_{3\text{-}a}$), 123.5–137.7 (C_{arom}), 140.1 (C_6), 142.1 ($C_{7\text{-}a}$), 147.1 (C_3), 156.6 ($C_{5'}$), 160.2 (C_9), 161.2 (C_4), 166.6 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{26}H_{24}N_5O_4)^+$ 470.1780, found 470.1784.

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*4.7.2. Ethyl 5-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-3-methyl-4-oxo-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylate (**11b**)*

White crystals, yield 78%, mp: 147–149 °C; IR (KBr, cm^{-1}): 1678 (C═O), 1620 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, 3H, J = 7.2 Hz, —O—CH_2—CH_3), 2.71 (s, 3H, H_8), 4.52 (q, 2H, J = 6.9 Hz, —O—CH_2—CH_3), 5.66 (s, 2H, N—CH_2), 6.60 (s, 1H, $H_{4'}$), 7.34–8.01 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.04 (—O—CH_2—CH_3), 13.36 (C_8), 37.9 (N—CH_2), 63.3 (O—CH_2—CH_3), 101.3 ($C_{4'}$), 111.1 ($C_{3\text{-}a}$), 121.5–137.7 (C_{arom}), 140.2 (C_6), 143.1 ($C_{7\text{-}a}$), 147.09 (C_3), 157.6 ($C_{5'}$), 160.5 (C_9), 161.3 (C_4), 166.6 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{25}H_{21}ClN_5O_4)^+$ 490.1282, found 490.1294.

*4.7.3. Ethyl 5-((3-(4-methoxyphenyl)isoxazol-5-yl)methyl)-3-methyl-4-oxo-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylate (**11c**)*

White crystals, yield 78%, mp: 144–146 °C; IR (KBr, cm^{-1}): 1677 (C═O), 1618 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, 3H, J = 7.2 Hz, —O—CH_2—CH_3), 2.69 (s, 3H, H_8), 3.58 (s, 3H, CH_3), 4.54 (q, 2H, J = 6.9 Hz, —O—CH_2—CH_3), 5.64 (s, 2H, N—CH_2), 6.61 (s, 1H, $H_{4'}$), 7.36–8.04 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.01 (—O—CH_2—CH_3), 13.40 (C_8), 38.1 (N—CH_2), 54.2 (CH_3), 63.6 (O—CH_2—CH_3), 101.2 ($C_{4'}$), 111.0 ($C_{3\text{-}a}$), 122.5–137.8 (C_{arom}), 141.7 (C_6), 143.2 ($C_{7\text{-}a}$), 147.1 (C_3), 157.8 ($C_{5'}$), 160.6 (C_9), 161.7 (C_4), 166.8 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{26}H_{24}N_5O_5)^+$ 486.1730, found 486.1733.

*4.7.4. Ethyl 5-((3-(4-isopropylphenyl)isoxazol-5-yl)methyl)-3-methyl-4-oxo-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylate (**11d**)*

White crystals, yield 80%, mp: 138–140 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1620 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 6H, —CH-(CH_3)$_2$), 1.46 (t, 3H, J = 7.2 Hz, —O—CH_2—CH_3), 2.72 (s, 3H, H_8), 2.93 (m, 1H, —CH—(CH_3)$_2$), 4.51 (q, 2H, J = 6.9 Hz, —O—CH_2—CH_3), 5.67 (s, 2H, N—CH_2), 6.59 (s, 1H, $H_{4'}$), 7.23–8.04 (m, 9H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.01 (—O—CH_2—CH_3), 13.36 (C_8), 23.3 (—CH—(CH_3)$_2$), 32.7 (—CH—(CH_3)$_2$), 37.8 (N—CH_2), 63.3 (O—CH_2—CH_3), 101.4 ($C_{4'}$), 110.0 ($C_{3\text{-}a}$), 121.5–148.5 (C_{arom}), 141.7 (C_6), 143.2 ($C_{7\text{-}a}$), 154.7 (C_3), 156.8 ($C_{5'}$), 160.6 (C_9), 163.3 (C_4), 166.0 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{28}H_{28}N_5O_4)^+$ 498.2080, found 498.2087.

*4.7.5. 3-Methyl-1-phenyl-5-((3-p-tolylisoxazol-5-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**12a**)*

White crystals, yield 80%, mp: 142–144 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1620 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.69 (s, 3H, H_8), 5.33 (s, 2H, N—CH_2), 6.67 (s, 1H, $H_{4'}$), 7.30–8.01 (m, 9H, Ar—H), 8.19 (s, 1H, H_6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (C_8), 20.9 (CH_3), 39.8 (N—CH_2), 101.8 ($C_{4'}$), 104.9 ($C_{3\text{-}a}$), 121.6–140.0 (C_{arom}), 146.7 ($C_{7\text{-}a}$), 148.2 (C_6), 150.9 (C_3), 156.7 ($C_{5'}$), 162.4 (C_4), 165.4 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{23}H_{19}N_5O_2)^+$ 398.1605, found 398.1617.

*4.7.6. 5-((3-(4-Chlorophenyl)isoxazol-5-yl)methyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**12b**)*

White crystals, yield 70%, mp: 148–150 °C; IR (KBr, cm^{-1}): 1678 (C═O), 1618 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.70 (s, 3H, H_8), 5.38 (s, 2H, N—CH_2), 6.65 (s, 1H, $H_{4'}$), 7.29–8.1 (m, 9H, Ar—H), 8.21 (s, 1H, H_6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (C_8), 39.6 (N—CH_2), 99.9 ($C_{4'}$), 105.1 ($C_{3\text{-}a}$), 121.4–140.1 (C_{arom}), 146.6 ($C_{7\text{-}a}$), 148.1 (C_6), 150.8 (C_3), 156.5 ($C_{5'}$), 162.1 (C_4), 165.4 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{22}H_{17}ClN_5O_2)^+$ 418.1020, found 418.1024.

*4.7.7. 5-((3-(4-Methoxyphenyl)isoxazol-5-yl)methyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**12c**)*

White crystals, yield 73%, mp: 140–142 °C; IR (KBr, cm^{-1}): 1680 (C═O), 1615 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 2.70 (s, 3H, H_8), 3.82 (s, 3H, —OCH_3), 5.30 (s, 2H, N—CH_2), 6.66 (s, 1H, $H_{4'}$), 7.27–8.0 (m, 9H, Ar—H), 8.20 (s, 1H, H_6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (C_8), 20.9 (CH_3), 39.6 (N—CH_2), 54.8 (—OCH_3), 101.6 ($C_{4'}$), 105.1 ($C_{3\text{-}a}$), 121.4–139.8 (C_{arom}), 146.5 ($C_{7\text{-}a}$), 148.3 (C_6), 149.9 (C_3), 156.5 ($C_{5'}$), 162.1 (C_4), 165.3 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{23}H_{20}N_5O_3)^+$ 414.1518, found 414.1521.

*4.7.8. 5-((3-(4-Isopropylphenyl)isoxazol-5-yl)methyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**12d**)*

White crystals, yield 78%, mp: 136–138 °C; IR (KBr, cm^{-1}): 1679 (C═O), 1620 (isoxazole C═N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 6H, —CH—(CH_3)$_2$), 2.73 (s, 3H, H_8), 2.95 (m, 1H, —CH—(CH_3)$_2$), 5.30 (s, 2H, N—CH_2), 6.66 (s, 1H, $H_{4'}$), 7.27–8.0 (m, 9H, Ar—H), 8.20 (s, 1H, H_6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (C_8), 20.9 (CH_3), 39.6 (N—CH_2), 54.8 (—OCH_3), 101.6 ($C_{4'}$), 105.1 ($C_{3\text{-}a}$), 121.4–139.8 (C_{arom}), 146.5 ($C_{7\text{-}a}$), 148.3 (C_6), 149.9 (C_3), 156.5 ($C_{5'}$), 162.1 (C_4), 165.3 ($C_{3'}$). HRMS $[M+H]^+$ calcd for $(C_{25}H_{24}N_5O_2)^+$ 426.1880, found 426.1885.

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